

SupraBox: a New Class of Chiral Supramolecular Oxazoline Ligands

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Dedicated to Prof Cesare Gennari on the occasion of his 60th birthday

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A new class of oxazoline ligands, named SupraBox, was studied. These ligands possess an additional urea functionality to generate supramolecular bidentate ligands in transition metal complexes, by the establishment of hydrogen bonds between the urea N-H hydrogens of one ligand and the carbonyl oxygen of a second one. A library of 16 SupraBox ligands was prepared containing five differently substituted oxazoline nuclei, four linkers and three different urea substituents.

The formation of copper(II) and palladium(II) complexes was investigated by MS, UV-Vis and ¹H-NMR spectroscopy. The SupraBox library was screened in the copper catalyzed asymmetric benzoylation of *vic*-diols. Good selectivities were obtained in the kinetic resolution of racemic hydrobenzoin (*ee* up to 86% and selectivity (*s*) = 28) and in the desymmetrization of *meso*-hydrobenzoin (*ee* up to 88%).

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Introduction

The supramolecular assembly of biologically active species through hydrogen bonding is a widely occurring phenomenon in nature, as exemplified by DNA base pairing, the secondary or tertiary structure of proteins or the mechanism of action of many enzymes. Taking inspiration from nature, chemists have designed and realized supramolecular catalysts in which a receptor or a cavitand is connected to an active site.^[1] In a closely related approach, chiral ligands for transition metals were also developed which possess, besides centers for coordinating to a metal ion an additional functionality that is capable of ligand-ligand bonding via non-covalent interactions, such as hydrogen bonding or coordinative bonding. These ligands are usually referred to as "supramolecular bidentate ligands".^[2] This approach causes reduced degrees of freedom in the resulting metal coordination complexes with respect to analogous monodentate ligands, which is expected to afford a more pre-organized system with better capacity of controlling the subsequent metal-catalyzed reaction.

Among the different kinds of non-covalent interactions that have been used so far for developing supramolecular ligands, hydrogen bonds are arguably the most practical and efficient for several reasons: (i) functional groups capable of hydrogen bonding (e.g.

amides, ureas, guanidines) are stable and relatively easy-to-introduce; (ii) hydrogen bonds are created dynamically and reversibly in the reaction medium (where catalysis is to take place), being able to self-repair when broken, and often coexist with other interactions in a 'non-invasive' manner. In the last years several powerful supramolecular bidentate ligands were described with outstanding reactivity and selectivity but, unfortunately, this methodology has thus far been exclusively confined to the use of phosphorus ligands.^[2]

We herein report the first example of H-bond-induced assembly of monodentate oxazolines for the formation of supramolecular bis(oxazoline) metal complexes, and the application of the their copper(II) complexes in Cu(II) asymmetric catalytic transformations.^[3]

Results and Discussion

Bis(oxazolines) (box) have developed into one of the most useful ligand classes for asymmetric catalysis owing to their ability to coordinate a large variety of metal ions which can be attained in a great number of catalytic processes with excellent reactivity and selectivity.^[4] The general structural motif of these ligands can be described as two oxazoline units being connected by a wide range of linkers. These linkers tune the distance and the bite angle of the two oxazolines, and might also introduce additional stereogenic elements (centers or axes) to optimize the enantioselectivity of a given asymmetric reaction.

In our approach, a covalent linker is replaced by a hydrogen-bond interaction between two urea moieties that are connected to the oxazoline rings via different spacers (Figure 1). The urea functionality has been used before as a self-complementary recognition motif in the formation of supramolecular bidentate phosphine and phosphite ligands.^[5]

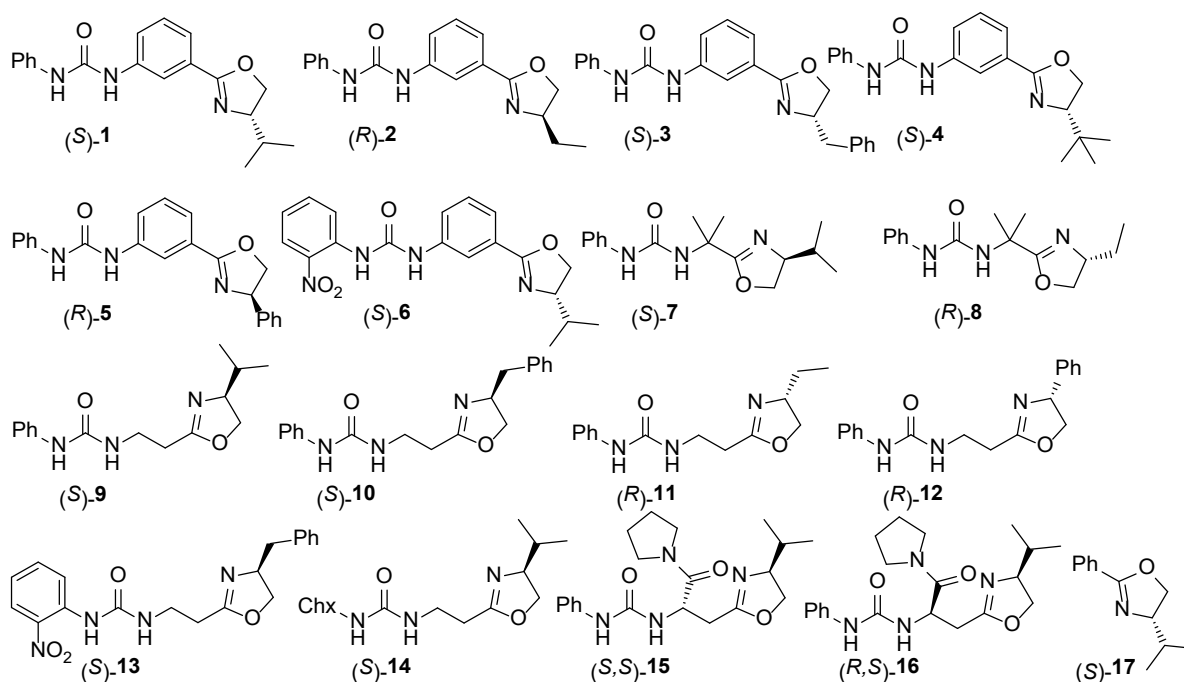


Figure 2. The SupraBox ligand library.

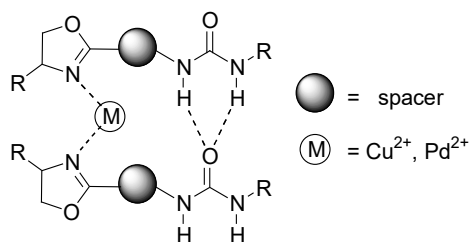
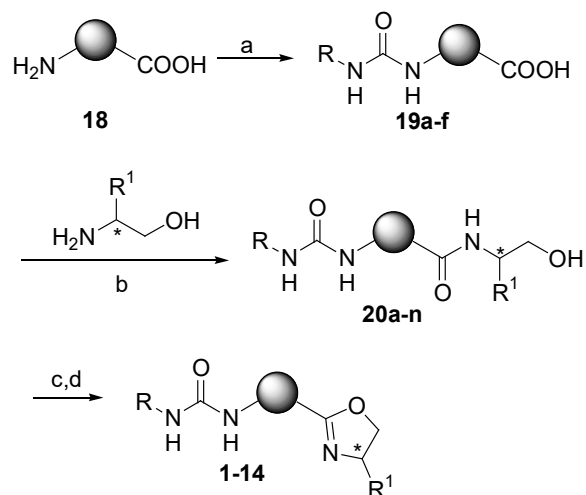


Figure 1. SupraBox: general structure of the ligands and of the supramolecular bidentate complex.

The synthesis of a library of “SupraBox” ligands (**1-16**, Figure 2) was thus planned. Their structure allows a modular synthetic approach and the introduction of several sites of diversity for a steric and electronic tuning of the ligand properties: (i) the spacer between the oxazoline and the urea moiety, (ii) the substitution at the oxazoline stereocenter, (iii) the substitution pattern on the urea moiety.

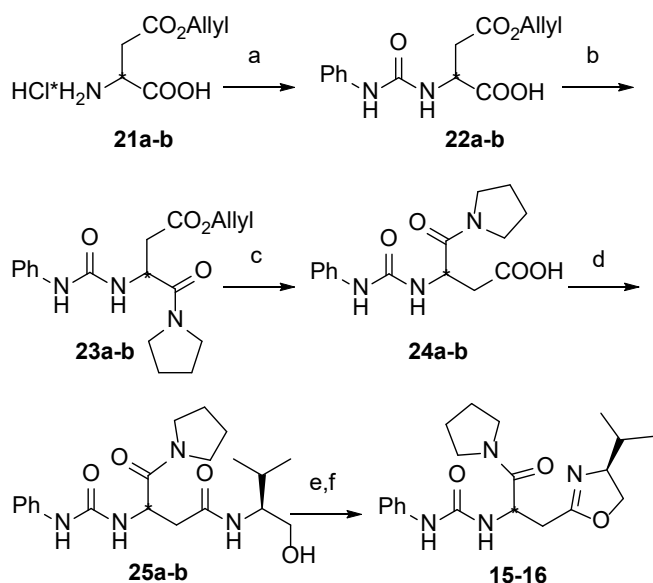
Synthesis of the ligands

The ligands were prepared following a straightforward and reliable synthetic protocol involving only one or two chromatographic purifications (Schemes 1 and 2). For the synthesis of ligands **1-14** (Scheme 1), the amino acid linkers **18** were reacted in THF or, in case of limited solubility of the substrate, in 2 N NaOH, with different isocyanates to give the corresponding acid ureas **19**.^[6] These were then coupled to amino alcohols using HBTU in DCM. The ring closure and formation of the oxazolines **1-14** was achieved in good yields using DAST, which was required to be employed in excess (2.2 equiv), probably because of an interference with the urea moiety.



Scheme 1. Synthesis of the SupraBox ligands: a) RNCO (1 equiv), THF or aq-NaOH, 60-70 %; b) *i*-Pr₂EtN (2.5 equiv), HBTU (1.3 equiv), aminoalcohol (1.2 equiv), DCM, 0 °C to r.t., 16 h, 85-99 %; c) DAST (2.2 equiv.), THF, -78 °C to r.t.; d) K₂CO₃ 75-90 %.

For the synthesis of ligands **15** and **16**, featuring the aspartic α -pyrrolidinamide linker, a slightly different protocol was followed (Scheme 2). Starting from L- or D-aspartic acid β -allyl ester **21**^[7] the corresponding phenyl urea **22** was assembled and then reacted with pyrrolidine to obtain the α -pyrrolidinamide derivative **23**. The allyl ester was cleaved by reaction with [Pd(PPh₃)₄] / pyrrolidine, and the resulting β -carboxylic acid was transformed into the oxazoline nucleus by reaction with (*S*)-valinol and DAST-mediated ring closure.



Scheme 2. Synthesis of ligands **15** and **16**: a) PhNCO (1 equiv.), Et₃N (1 equiv), THF, r.t., 88%; b) *i*-Pr₂EtN (2.5 equiv), HBTU (1.3 equiv), pyrrolidine (1.2 equiv), DMF, 78 %; c) pyrrolidine (1.2 equiv), Ph₃P (0.18 equiv), [Pd(Ph₃P)] (0.04 equiv), DCM, 77 %; d) *i*-Pr₂EtN (2.5 equiv), HBTU (1.3 equiv), L-valinol (1.2 equiv), DCM, 60 %; e) DAST (2.2 equiv), THF, -78 °C to r.t.; f) K₂CO₃ 58 %.

Overall, four different amino acid spacers (β -alanine, 2-amino-*iso*-butyric acid, *m*-amino benzoic acid and aspartic acid α -pyrrolidine-carboxamide) were used to impart different conformational rigidity to the ligands and hence influence the formation of the intramolecular hydrogen bonds between the urea moieties. In addition, three different isocyanates were included in the screening to vary the H-bond forming properties of the ligands, as well as five aminoalcohols derived from natural α -amino acids to tune the transfer of the stereochemical information. In this way a small collection of 16 ligands was prepared for testing.

Complexation studies

Before screening the library of ligands in catalytic applications, we set out to investigate the formation of transition metal complexes of the SupraBox ligands. The structures of complexes of supramolecular bidentate ligands containing additional functionalities capable of H-bonding interactions have usually been assessed spectroscopically^[8,6] by ¹H, ¹³C, and ³¹P-NMR. ESI-MS was also used, since this ionization methodology allowed the detection of the ion of the self-assembled complex, as well as X-ray structural analysis which showed the self-organized complex, held together by noncovalent interactions (metal coordination, intermolecular hydrogen bonds, and π -stacking).

The copper(II) complex of ligand (*S*)-**9** was obtained by treatment with CuCl₂ in CH₂Cl₂, followed by recrystallization of the crude material from CH₂Cl₂/*n*-hexane. Its molecular composition was assessed by ESI-MS spectroscopy, which revealed one principal peak at *m/z* 613.3, corresponding to a copper(I) atom coordinated to two molecules of ligand, i.e. [CuL₂]⁺. The reduction of Cu²⁺ to Cu⁺ has been reported to occur using ESI as ionization source.^[9] The presence of two ligands coordinated to Cu²⁺ was further confirmed by a measurement of the complex absorbance as a function of the ligand/metal ratio, also known as Yoe-Jones method^[10] (Figure 3). This plot resulted in a quasi-linear increase of the complex absorbance value, up to the

combining ratio of 2:1. Further addition of the ligand produced an almost negligible variation of the absorbance. The deviation from linearity could depend on the stability of the complex with respect to ligand dissociation:¹¹ the more stable the complex, the closer the experimental curve approaches a straight line.

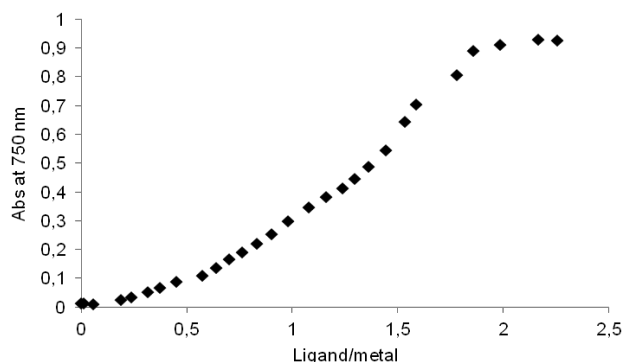


Figure 3. Yoe-Jones plot of complex absorbance as a function of ligand/metal ratio of complex [Cu(**9**)₂Cl₂]. Ligand (*S*)-**9** was added in accurately weighed portions were added to CuCl₂ in CH₂Cl₂ and UV absorption spectra were recorded after each addition.

The formation of palladium(II) complexes was also investigated: palladium chloride was reacted with two equiv of ligand (*S*)-**9** in dichloromethane and the complex [Pd(*S*)-**9**]₂Cl₂ was isolated by precipitation from hexanes. Since in this case the complex is diamagnetic, the supramolecular bidentate ligand Pd(*S*)-**9**]₂Cl₂ could be studied by ¹H-NMR. It is important to note that only one set of signals could be detected in the NMR spectra at room temperature, and the two coordinated molecules of **9**, i.e. the one acting as hydrogen bond donor and the other as acceptor (Figure 4), could not be distinguished. The hydrogen bonding state of the NH protons for both the free ligand and the Pd-complex was also studied, and in particular the variation of the chemical shift of the N-H signals upon dilution was considered for both the ligand and the Pd-complex. The signals of the NH of the complex showed a higher chemical shift than those of the free ligand at 5 mM (5.74 vs 5.62 ppm for NH_A and 7.03 vs 6.80 ppm for NH_B) together with a lower concentration dependence over the 5–40 mM range ($\Delta\delta$ = 0.1 vs 0.27 ppm for NH_A and $\Delta\delta$ = 0.1 vs 0.32 ppm for NH_B, see the Supporting Information for the values and graphics). The temperature dependence of the NH signals was also investigated, but in this case the signals broadened and coalesced upon cooling and two signals appeared at temperature lower than 268 K, which hampered the measurement of the temperature coefficient ($\Delta\delta/\Delta T$) of each NH proton. These experiments, which are commonly used to differentiate between random-coil peptides and peptides in hydrogen bonded conformations,^[12] indicate that the two ligands coordinated to the metal atom interact intramolecularly via hydrogen bonds.

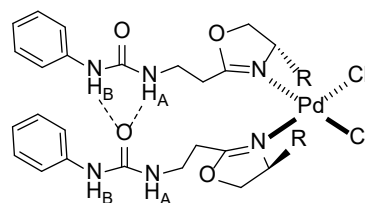


Figure 4. SupraBox: general structure of the ligands and of the supramolecular bidentate complex.

Enantioselective catalytic applications

Copper bis(oxazoline) complexes have been shown to be efficient catalysts in the kinetic resolution of racemic diols,^[13] and in particular of hydrobenzoin, by benzoylation.^[14] For this reason we decided to screen ligands **1-16** in this reaction (Table 1).

In addition mono(oxazoline) **17**^[15] (Figure 2) devoid of functional groups capable of forming hydrogen bonds was added to the screening to validate the importance of the supramolecular interaction.

Table 1. Screening of the SupraBox ligands in the copper catalyzed enantioselective benzoylation of hydrobenzoin **23**.^[a]

Reaction scheme for Table 1: Hydrobenzoin (racemic diol) reacts with benzoyl chloride (a) to form (R,R)-26 and (S,S)-26.

Entry	Ligand	Yield (%) ^[b]	ee (%) ^[c] (conf.) ^[d]	Selectivity (s) ^[e]
1	(S)-1	17	12 (R,R)	1.3
2	(R)-2	35	0	1.0
3	(S)-3	38	34 (R,R)	2.5
4	(S)-4	39	14 (R,R)	1.4
5	(R)-5	28	14 (S,S)	1.4
6	(S)-6	34	20 (R,R)	1.7
7	(S)-7	44	64 (R,R)	7.4
8	(R)-8	26	56 (S,S)	4.3
9	(S)-9	44	86 (R,R)	27
10	(S,S)-15	43	70 (R,R)	9.5
11	(R)-11	45	86 (S,S)	28
12	(R)-12	47	20 (S,S)	1.8
13	(S)-13	45	2 (R,R)	1.1
14	(S)-14	41	44 (R,R)	3.4
15	(S,S)-15	37	22 (R,R)	1.8
16	(R,S)-16	35	36 (R,R)	2.5
17	(R,R)-Ph-Box ^[f]	48	>99 (S,S)	>645 ^[g]
18	(S)-17	40	0	1.0

[a] Reagents and conditions: 5-mol% CuCl₂, 10-mol% ligand, 0.5 equiv PhCOCl, 1 equiv *i*PrEt₃N, CH₂Cl₂, 3 h, 0 °C. [b] Isolated yield after chromatography. [c] Determined by chiral HPLC. [d] Determined according to ref. 14. [e] determined according to ref. 16. [f] (R,R)-Ph-Box = 2,2-Isopropylidenebis[(4R)-4-phenyl-2-oxazoline] [g] See ref. [14a]

The catalytic reactions were carried out by pre-formation of the complexes by stirring a suspension of CuCl₂ in a solution of the ligand in CH₂Cl₂, until all of the highly insoluble copper salt becomes soluble by complexation (formation of a deeply colored solution) with the ligand. Despite structural similarities between **1-16**, their performance in the asymmetric benzoylation varied considerably, and rather surprisingly, best selectivities were obtained with ligands **9** and **11**, while ligands **10** and **12** having benzyl and phenyl substitution at the stereocenters, that had proven most successful in the title reaction with bis(oxazolines),^[13,14] gave inferior results. From a closer inspection of the selectivities, the importance of a fine balance of conformational flexibility, steric hindrance, and electronic properties becomes evident. In particular, the *meta*-disubstituted aromatic linker (entries 1-6) and the C α -tetrasubstituted amino acid (Aib) hamper enantioselectivity, probably because of the high rigidity which does not allow an efficient docking of the two urea functionalities. In fact, the use of a β -alanine linker (entries 9-14), which is best combined with an *iso*-propyl or ethyl substitution at the oxazoline moiety, results in a

significant increase of selectivity (entries 9 and 11 respectively). Finally, no selectivity was obtained with the monodentate ligand **17**, which is not capable of supramolecular interactions (entry 18).

The asymmetric catalytic acylation with copper(II) complexes has also been applied to the desymmetrization of *meso*-diols,^[17] although with lower *ees* than the kinetic resolution (*ee* = 58% in the asymmetric benzoylation of *meso*-hydrobenzoin^[17a]). We tested a selection of ligands in the desymmetrization of *meso*-hydrobenzoin by benzoylation and the results are collected in Table 2.

Table 2. Screening of the SupraBox ligands in the copper catalyzed desymmetrization of *meso*-hydrobenzoin by benzoylation.^[a]

Reaction scheme for Table 2: *meso*-hydrobenzoin reacts with benzoyl chloride (a) to form (1R,2S)-27 and (1S,2R)-27.

Entry	Ligand	Yield (%) ^[b]	ee (%) ^[c] (conf) ^[d]
1	(S)-1	68	2 (1R,2S)
2	(R)-5	74	7 (1S,2R)
3	(S)-7	88	68 (1R,2S)
4	(R)-8	99	26 (1S,2R)
5	(S)-9	44	88 (1R,2S)
6	(S)-10	77	6 (1R,2S)
7	(R)-11	92	78 (1S,2R)
8	(R)-12	70	24 (1S,2R)
9	(S)-14	89	38 (1R,2S)
10	(S,S)-15	68	40 (1R,2S)
11	(R,S)-16	62	20 (1R,2S)
12	(R,R)-Ph-Box ^[e]	86	59 ^[f]
13	(S)-17	73	0

[a] Reagents and conditions: 5 mol% CuCl₂, 10-mol% ligand, 0.5 equiv PhCOCl, 1 equiv *i*PrEt₃N, CH₂Cl₂, 3 h, 0 °C. [b] Isolated yield after chromatography. [c] Determined by chiral HPLC. [d] Determined according to ref. 17a. [e] (R,R)-Ph-Box = 2,2-Isopropylidenebis[(4R)-4-phenyl-2-oxazoline] [f] See to ref. 17a

Once again satisfactory results were obtained with ligands **9** and **11** (entries 5 and 7). Notably, the SupraBox ligands outperform the classical methylene-bridged bis(oxazolines) and the *aza*-bis(oxazolines), probably because the flexibility of the linker allows these *meso*-substrates to be accommodated in the copper(II) coordination sphere. On the contrary, the rigidity of the classical bis(oxazolines) creates a cavity where the *C*₂-symmetric (*dl*)-*vic*-diols can fit better than the σ -symmetric *meso*-diols. Also in this case, ligand **17**, devoid of functionalities acting as hydrogen bond donors, catalyzed the benzoylation in an unselective way (entry 13).

Conclusions

A new class of supramolecular bidentate nitrogen ligands has been investigated. These ligands feature a chiral oxazoline ring and a urea functionality linked by a spacer. A library of 16 members was prepared containing five differently substituted oxazoline nuclei, four linkers and three different urea substituents. The coordination of these ligands to copper(II) and palladium(II) ions was studied, revealing that: i) two ligands coordinate to the metal ions via their oxazoline nitrogens; ii) the N-Hs of the urea moiety are intramolecularly hydrogen-bonded as indicated by the downfield values of their chemical shift as well as their low

concentration dependence. The SupraBox library was screened in the kinetic resolution of racemic hydrobenzoin and desymmetrization of *meso*-hydrobenzoin by copper-catalyzed benzoylation. Good selectivities (*s*) were obtained in the case of the kinetic resolution, while the use of SupraBox ligands proved particularly beneficial in the case of the desymmetrization of hydrobenzoin, outperforming classical bis(oxazolines).

Further studies are currently underway to extend the scope of application for this new class of ligands.

Experimental Section

General Remarks. All reactions were carried out in flame-dried glassware with magnetic stirring under nitrogen atmosphere, unless otherwise stated. Dry solvents (over molecular sieves in bottles with crown cap) were purchased from Fluka and stored under nitrogen. The reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F₂₅₄ pre-coated glass plates (0.25 mm thickness). Visualization was accomplished by irradiation with a UV lamp and/or staining with a potassium permanganate alkaline solution. Flash column chromatography was performed using silica gel 60 Å, particle size 40–64 µm, following the procedure by Still and co-workers.^[18] Proton NMR spectra were recorded on a spectrometer operating at 400.13 MHz. Proton chemical shifts are reported in ppm (δ) with the solvent reference relative to tetramethylsilane (TMS) employed as the internal standard (CDCl₃, δ = 7.26 ppm; [D₆]DMSO, δ = 2.50 ppm; CD₃OD, δ = 3.33 ppm). The following abbreviations are used to describe spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal, dd = doublet-doublet. ¹³C NMR spectra were recorded on a 400 MHz spectrometer operating at 100.56 MHz, with complete proton decoupling. Carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard (CDCl₃, δ = 77.23 ppm; [D₆]DMSO, δ = 39.51 ppm; CD₃OD, δ = 49.05 ppm). Infrared spectra were recorded on a standard FT/IR spectrometer. Optical rotation values were measured on an automatic polarimeter with a 1 dm cell at the sodium D line (λ = 589 nm). HPLC was performed on an instrument equipped with a diode array detector, using a chiral column. High resolution mass spectra (HRMS) were performed on a Fourier Transform Ion Cyclotron Resonance (FT-ICR) Mass Spectrometer APEX II & Xmass software (Bruker Daltonics) – 4.7 T Magnet (MagneX) equipped with ESI source, available at CIGA (Centro Interdipartimentale Grandi Apparecchiature) c/o Università degli Studi di Milano. Low resolution mass spectra (MS) were acquired either on a Thermo-Finnigan LCQ Advantage mass spectrometer (ESI ion source) or on a VG Autospec M246 spectrometer (FAB ion source). Elemental analyses were performed on a Perkin Elmer Series II CHNS/O Analyzer 2000.

Materials. Commercially available reagents were used as received. 4-aspartic acid β-allyl ester^[7] (**21**) and (*S*)-4-isopropyl-2-phenyl-4,5-dihydrooxazole^[15] (**17**) were prepared according to literature procedures.

3-(3-Phenylureido)benzoic acid (19a). Phenylisocyanate (1.59 mL, 14.5 mmol, 1.0 equiv.) and 3-aminobenzoic acid (2.0 g, 14.5 mmol, 1.0 equiv.) were dissolved in 80 mL THF and the reaction mixture stirred at room temperature for 3 days. The mixture was treated with cold Et₂O to provide the precipitation of the product as fine white powder (2.34 g, 9.15 mmol, 63%).

R_f = 0.35 (DCM/MeOH 95:5) — m.p. 152–153 °C — ¹H NMR (400 MHz, CD₃OD, 25 °C): δ = 7.03 (m, 1H), 7.30 (m, 2H), 7.37–7.46 (m, 3H), 7.68 (ddd, 1H, *J* = 7.7, 1.5, 1.1 Hz), 7.73 (ddd, 1H, *J* = 8.0, 2.3, 1.1 Hz), 8.08 (t, 1H, *J* = 1.7 Hz). — ¹³C NMR (100.6 MHz, CD₃OD, 25 °C): δ = 119.1, 119.9, 122.6, 123.2, 123.5, 128.4, 128.6, 131.2, 139.0, 139.5, 151.1, 168.2. — **IR:** ν = 3354, 2724, 1738, 1680, 1649, 1556, 1310, 1156, 1066. —

C₁₄H₁₂N₂O₃ (256.26): calcd. C 65.62; H 4.72; N 10.93; found C 63.38, 4.44, 10.81.

3-(3-(2-Nitrophenyl)ureido)benzoic acid (19b). 2-nitrophenyl isocyanate (1.0 g, 6.09 mmol, 1.0 equiv.) and 3-aminobenzoic acid (0.84 g, 6.09 mmol, 1.0 equiv.) were dissolved in 60 mL THF and the reaction mixture stirred at room temperature for 3 days. The mixture was treated with cold Et₂O to provide the precipitation of the product as fine yellow powder (1.36 g, 4.50 mmol, 74%).

R_f = 0.26 (DCM/MeOH 95:5) — m.p. 174–175 °C — ¹H NMR (400 MHz, DMSO, 25 °C): δ = 7.22 (ddd, 1H, *J* = 8.4, 7.2, 1.2 Hz), 7.42 (t, 1H, *J* = 7.8 Hz), 7.59 (dt, 1H, *J* = 7.7, 1.2 Hz), 7.66–7.73 (m, 2H), 8.09 (dd, 1H, *J* = 8.4, 1.6 Hz), 8.15 (t, 1H, *J* = 1.8 Hz), 8.29 (dd, 1H, *J* = 8.5, 1.2 Hz), 9.61 (s, 1H), 10.03 (s, 1H), 12.93 (s, 1H). — ¹³C NMR (100.6 MHz, DMSO, 25 °C): δ = 119.7, 122.8, 123.0, 123.7, 125.8, 129.6, 131.9, 135.2, 135.4, 138.3, 140.0, 152.3, 167.6. — **IR:** ν = 3354, 3281, 2724, 1829, 1739, 1652, 1543, 1310, 1155, 1073, 949. — C₁₄H₁₁N₃O₅ (301.25): calcd. C 55.82; H 3.68; N 13.95; found C 55.54, H 3.34, N 14.30.

2-Methyl-2-(3-phenylureido)propanoic acid (19c). 2-Aminoisobutyric acid (3.0 g, 29 mmol, 1.3 equiv.) was suspended in 10 mL of 2 M NaOH then phenylisocyanate (2.37 mL, 22 mmol, 1.0 equiv.) was added and the mixture reaction was stirred for 60 minutes at room temperature. The mixture was filtered and the product was precipitated from solution by slow addition of 1 M HCl. The white solid was dissolved in 10 mL of 1 M NaOH and the solution washed with DCM. Addition of 1 M HCl provides the precipitation of product **1d** as fine white powder (1.73 g, 7.78 mmol, 35%). R_f = 0.37 (DCM/MeOH 95:5) — m.p. 157–158 °C — ¹H NMR (400 MHz, CD₃OH, 25 °C): δ = 1.53 (s, 6H), 6.41 (s, 1H), 6.95 (m, 1H), 7.24 (m, 2H), 7.30 (m, 2H), 8.19 (s, 1H). — ¹³C NMR (100.6 MHz, CD₃OD, 25 °C): δ = 24.6, 55.3, 118.6, 121.9, 128.3, 139.4, 155.7, 177.3. — **IR:** ν = 3381, 2724, 1704, 1648, 1544, 1308, 1158, 1069. — C₁₁H₁₄N₂O₃ (222.24): calcd. C 59.45; H 6.35; N 12.60; found C 59.55, H 5.55, N 12.61.

3-(3-Phenylureido)propanoic acid (19d). Phenylisocyanate (5.0 mL, 44 mmol, 1.0 equiv.) was dissolved in 220 mL THF and then β-alanine (3.92 g, 44 mmol, 1.0 equiv.) was added and the reaction mixture stirred at room temperature for 3 days. The mixture was treated with cold Et₂O to provide the precipitation of the product. After filtration the crude product was purified by flash chromatography eluting with 3→10% MeOH in DCM to yield product **1a** as fine white powder (8.33 g, 40 mmol, 91%).

R_f = 0.24 (DCM/MeOH 95:5) — m.p. 160–161 °C — ¹H NMR (400 MHz, CD₃OD, 25 °C): δ = 2.55 (t, 2H, *J* = 6.3 Hz), 3.47 (t, 2H, *J* = 6.3 Hz), 6.98 (t, 1H, *J* = 6.8 Hz), 7.25 (dd, 2H, *J* = 8.4, 7.4 Hz), 7.33 (m, 2H). — ¹³C NMR (100.6 MHz, CDCl₃, 25 °C): δ = 34.1, 35.2, 119.0, 122.0, 128.4, 139.5, 156.8, 174.3. — **IR:** ν = 3584, 3329, 2725, 1694, 1638, 1571, 1108. — C₁₀H₁₂N₂O₃ (208.21): calcd. C 57.68, H 5.81, N 13.45; found C 57.73, H 5.57, N 13.81.

3-(3-(2-Nitrophenyl)ureido)propanoic acid (19e). 2-Nitrophenylisocyanate (1.000 g, 6.09 mmol, 1.0 equiv.) was dissolved in 30 mL THF and then β-alanine (1.085 g, 12.18 mmol, 2.0 equiv.) was added and the reaction mixture stirred at room temperature for 3 days. The mixture was treated with cold Et₂O to provide the precipitation of the product. After filtration the crude product was purified by flash chromatography eluting with 3→5% MeOH in DCM to yield product **1b** as fine yellow powder (1.077 g, 4.25 mmol, 67%).

R_f = 0.41 (DCM/MeOH 95:5) — m.p. 160–161 °C — ¹H NMR (400 MHz, CDCl₃, 25 °C): δ = 2.56 (t, 2H, *J* = 6.6 Hz), 3.48 (t, 2H, *J* = 6.6 Hz), 7.13 (ddd, 1H, *J* = 8.5, 7.2, 1.3), 7.61 (ddd, 1H, *J* = 8.6, 7.2, 1.6), 8.12 (dd, 1H, *J* = 8.5, 1.6 Hz), 8.35 (dd, 1H, *J* = 8.6, 1.3 Hz). — ¹³C NMR (100.6 MHz, CD₃OD, 25 °C): δ = 33.8, 35.5, 121.4, 122.1, 125.1, 134.6, 135.7, 137.1, 155.4, 174.0. — **IR:** ν = 3583, 3393, 3330, 2753, 2360, 1694, 1611, 1582, 1539, 1342, 1258, 1142, 1085, 798. — C₁₀H₁₁N₃O₅ (253.21): calcd. C 47.43; H 4.38; N 16.59; found C 47.62, 4.23, 16.29.

3-(3-Cyclohexylureido)propanoic acid (19f). Cyclohexylisocyanate (2.86 mL, 22 mmol, 1.0 equiv.) was dissolved in 150 mL THF and then β-alanine

(2.00 g, 22.4 mmol, 1.0 equiv.) was added and the reaction mixture stirred at room temperature for 3 days. The mixture was treated with cold Et₂O to provide the precipitation of the product. After filtration the crude product was purified by flash chromatography eluting with 5→15% MeOH in DCM to yield product (**1e**) as fine white powder (3.60 g, 16.8 mmol, 76%).

$R_f = 0.23$ (DCM/MeOH 95:5) — m.p. 159–160 °C — ¹H NMR (400 MHz, [D₆]DMSO, 25 °C): δ = 0.97–1.16 (m, 3H), 1.18–1.30 (m, 2H), 1.50 (m, 1H), 1.61 (m, 1H), 1.70 (m, 1H), 2.31 (t, 2H, $J = 6.5$ Hz), 3.15 (q, 2H, $J = 6.5$ Hz), 5.74 (t, 1H, $J = 5.8$ Hz), 5.83 (d, 1H, 7.9 Hz), 12.17 (s, 1H). — ¹³C NMR (100.6 MHz, [D₆]DMSO, 25 °C): δ = 24.9, 25.8, 33.7, 35.5, 35.7, 48.1, 157.7, 173.9. — IR: ν = 3335, 1699, 1626, 1580, 1535, 1307, 1248, 1222, 1080, 921. — C₁₀H₁₈N₂O₃ (214.26): calcd. C 56.06; H 8.47; N 13.07; found C 55.87, H 8.62, N 12.72.

General procedure for the synthesis of products 20a–n. Acid **19** (1.1 equiv.) and *N,N*-diisopropylethylamine (3 equiv.) were dissolved in DCM (0.1 M solution) and the solution cooled at 0 °C. HBTU (1.3 equiv.) was added and the solution stirred at the same temperature for 30 minutes, then the aminoalcohol (1.0 equiv.) was added and the reaction mixture stirred at 0 °C for 60 minutes and overnight at room temperature. The solvent was evaporated under reduced pressure and the mixture separated by flash chromatography eluting with MeOH (gradient from 2 to 10%) in DCM to yield product **20**.

(S)-N-(1-Hydroxy-3-methylbutan-2-yl)-3-(3-phenylureido)benzamide (20a). According to the general procedure product **20a** was yielded as white solid (0.578 g, 1.69 mmol, 96%) starting from acid **19a** (0.500 g, 1.95 mmol) and coupled with L-valinol.

$R_f = 0.38$ (DCM/MeOH 95:5). — m.p. 167–168 °C — $[\alpha]_D^{20} = -44.37$ ($c = 0.1$, CHCl₃) — ¹H NMR (400 MHz, CD₃OD, 25 °C): δ = 1.00 (d, 3H, $J = 6.8$ Hz), 1.03 (d, 3H, $J = 6.8$ Hz), 2.00 (m, 1H), 3.67–3.76 (m, 2H), 3.91 (m, 1H), 7.03 (t, 1H, $J = 7.3$ Hz), 7.30 (m, 2H), 7.39 (t, 1H, $J = 7.9$ Hz), 7.44 (dd, 2H, $J = 8.7$, 1.2 Hz), 7.48 (dt, 1H, $J = 7.7$, 1.3 Hz), 7.58 (ddd, 1H, $J = 8.1$, 2.1, 1.0 Hz), 7.88 (t, 1H, $J = 1.8$ Hz). — ¹³C NMR (100.6 MHz, CD₃OD, 25 °C): δ = 17.8, 18.7, 28.9, 57.4, 61.7, 117.9, 119.0, 121.2, 121.8, 122.6, 128.4, 128.6, 135.7, 138.9, 139.4, 153.9, 169.2. — IR: ν = 3266, 3200, 2722, 1656, 1609, 1565, 1501, 1310, 1221, 1167, 1089, 989, 840. — C₁₉H₂₃N₃O₃ (341.40): calcd. C 66.84; H 6.79; N 12.31; found C 66.62, H 7.14, N 12.14.

(R)-N-(1-Hydroxybutan-2-yl)-3-(3-phenylureido)benzamide (20b). According to the general procedure product **20b** was yielded as white solid (0.565 g, 1.72 mmol, 97%) starting from acid **19a** (0.500 g, 1.95 mmol) and coupled with (R)-2-aminobutan-1-ol.

$R_f = 0.40$ (DCM/MeOH 95:5). — m.p. 146–147 °C — $[\alpha]_D^{20} = +42.58$ ($c = 0.1$, CHCl₃) — ¹H NMR (400 MHz, CD₃OD, 25 °C): δ = 1.00 (t, 3H, $J = 7.5$ Hz), 1.56 (m, 1H), 1.76 (m, 1H), 3.63 (dd, 2H, $J = 5.6$, 0.9 Hz), 4.03 (m, 2H), 7.03 (t, 1H, $J = 7.3$ Hz), 7.29 (dd, 2H, $J = 8.5$, 7.5 Hz), 7.36 (t, 1H, $J = 7.8$ Hz), 7.44 (dd, 2H, $J = 8.7$, 1.2 Hz), 7.48 (dt, 1H, $J = 7.7$, 1.3 Hz), 7.58 (ddd, 1H, $J = 7.9$, 2.2, 1.1 Hz), 7.88 (t, 1H, $J = 1.8$ Hz), 8.05 (d, 1H, $J = 8.3$ Hz). — ¹³C NMR (100.6 MHz, CD₃OD, 25 °C): δ = 9.6, 23.66, 53.7, 63.43, 117.9, 119.1, 121.2, 121.9, 122.6, 128.5, 128.7, 135.6, 138.9, 139.4, 153.9, 169.2. — IR: ν = 3383, 2724, 1697, 1648, 1542, 1154, 1069. — C₁₈H₂₁N₃O₃ (327.38): calcd. C 66.04; H 6.47; N 12.84; found C 65.93, H 6.70, N 12.58.

(S)-N-(1-Hydroxy-3-phenylpropan-2-yl)-3-(3-phenylureido)benzamide (20c). According to the general procedure product **20c** was yielded as white solid (0.689 g, 1.77 mmol, 100%) starting from acid **19a** (0.500 g, 1.95 mmol) and coupled with (S)-2-amino-3-phenylpropan-1-ol.

$R_f = 0.34$ (DCM/MeOH 95:5). — m.p. 157–158 °C — $[\alpha]_D^{20} = -50.29$ ($c = 0.1$, CHCl₃) — ¹H NMR (400 MHz, CD₃OD, 25 °C): δ = 2.87 (dd, 1H, $J = 13.7$, 8.6 Hz), 3.03 (dd, 1H, $J = 13.7$, 6.2 Hz), 3.66 (d, 2H, $J = 5.5$ Hz), 4.34 (m, 1H), 7.04 (t, 1H, $J = 7.5$ Hz), 7.17 (m, 1H), 7.29 (m, 6H), 7.37 (m, 2H), 7.45 (dd, 2H, $J = 8.6$, 1.0 Hz), 7.56 (dt, 1H, $J = 7.0$, 2.2 Hz), 7.79 (m, 1H). — ¹³C NMR (100.6 MHz, CD₃OD, 25 °C): δ = 36.6, 53.6, 62.9, 117.8, 119.0, 121.1, 121.8, 122.6, 125.9, 128.0, 128.5, 128.6, 129.0, 134.7, 135.5, 138.5,

139.0, 139.3, 153.9, 168.8. — IR: ν = 3324, 2724, 1739, 1648, 1543, 1310, 1265, 1155, 1069, 876, 840. — C₂₃H₂₃N₃O₃ (389.45): calcd. C 70.93; H 5.95; N 10.79; found C 70.88, H 6.18, N 7.78.

(S)-N-(1-Hydroxy-3,3-dimethylbutan-2-yl)-3-(3-phenylureido)benzamide (20d). According to the general procedure product **20d** was yielded as white solid (0.552 g, 1.55 mmol, 88%) starting from acid **19a** (0.500 g, 1.95 mmol) and coupled with (S)-2-amino-3,3-dimethylbutan-1-ol.

$R_f = 0.37$ (DCM/MeOH 95:5). — m.p. 97–98 °C — $[\alpha]_D^{20} = -49.69$ ($c = 0.1$, CHCl₃) — ¹H NMR (400 MHz, CD₃OD, 25 °C): δ = 1.02 (s, 9H), 3.63 (dd, 1H, $J = 11.4$, 8.8 Hz), 3.68 (dd, 1H, $J = 11.4$, 3.5 Hz), 4.04 (dd, 1H, $J = 8.8$, 3.5 Hz), 7.04 (m, 1H), 7.30 (m, 1H), 7.40 (t, 1H, $J = 7.7$ Hz), 7.42–7.50 (m, 3H), 7.59 (ddd, 1H, $J = 7.9$, 2.2, 1.1 Hz), 7.87 (t, 1H, $J = 1.7$ Hz). — ¹³C NMR (100.6 MHz, CD₃OD, 25 °C): δ = 26.0, 33.9, 54.4, 60.9, 117.9, 119.1, 121.3, 121.8, 122.6, 128.5, 128.7, 136.0, 138.9, 139.2, 153.9, 169.9. — IR: ν = 3278, 3204, 2727, 1670, 1625, 1589, 1553, 1500, 1310, 1233, 1134, 1088, 1047, 840. — C₂₀H₂₅N₃O₃ (355.43): calcd. C 67.58; H 7.09; N 11.82; found C 67.44, H 7.16, N 12.11.

(R)-N-(2-Hydroxy-1-phenylethyl)-3-(3-phenylureido)benzamide (20e). According to the general procedure product **20e** was yielded as white solid (0.420 g, 1.12 mmol, 98%) starting from acid **19a** (0.320 g, 1.25 mmol) and coupled with (R)-2-amino-2-phenylethanol.

$R_f = 0.39$ (DCM/MeOH 95:5). — m.p. 112–113 °C — $[\alpha]_D^{20} = -46.89$ ($c = 0.1$, CHCl₃) — ¹H NMR (400 MHz, CD₃OD, 25 °C): δ = 3.87 (d, 2H, $J = 6.6$ Hz), 5.21 (t, 1H, $J = 6.6$ Hz), 7.02 (t, 1H, $J = 7.3$ Hz), 7.23–7.45 (m, 10H), 7.51 (d, 1H, $J = 7.7$ Hz), 7.58 (dd, 1H, $J = 8.0$, 1.1 Hz), 7.90 (s, 1H). — ¹³C NMR (100.6 MHz, CD₃OD, 25 °C): δ = 56.4, 64.7, 118.0, 119.1, 121.3, 122.0, 122.6, 126.6, 127.0, 128.1, 128.5, 128.7, 135.3, 138.9, 139.4, 139.9, 153.9, 168.9. — IR: ν = 3300, 3205, 2727, 1646, 1621, 1599, 1563, 1348, 1298, 1235, 1175, 1065, 844. — C₂₂H₂₁N₃O₃ (375.42): calcd. C 70.38; H 5.64; N 11.19; found C 70.37, H 5.73, N 12.11.

(S)-N-(1-Hydroxy-3-phenylpropan-2-yl)-3-(3-(2-nitrophenyl)ureido)benzamide (20f). According to the general procedure product **20f** was yielded as yellow solid (0.568 g, 1.47 mmol, 97%) starting from acid **19b** (0.500 g, 1.66 mmol) and coupled with L-valinol.

$R_f = 0.36$ (DCM/MeOH 95:5). — m.p. 140–141 °C — $[\alpha]_D^{20} = -47.64$ ($c = 0.1$, CHCl₃) — ¹H NMR (400 MHz, CD₃OD, 25 °C): δ = 1.00 (d, 1H, $J = 6.8$ Hz), 1.03 (d, 1H, $J = 6.8$ Hz), 2.01 (m, 1H), 3.71 (m, 2H), 3.92 (m, 1H), 7.19 (ddd, 1H, $J = 8.4$, 7.4, 1.3), 7.42 (t, 1H, $J = 7.8$ Hz), 7.51 (dt, 1H, $J = 7.8$, 1.3 Hz), 7.67 (m, 2H), 7.97 (t, 1H, $J = 1.8$ Hz), 8.19 (dd, 1H, $J = 8.4$, 1.4 Hz), 8.48 (dd, 1H, $J = 8.6$, 1.2 Hz). — ¹³C NMR (100.6 MHz, CD₃OD, 25 °C): δ = 17.8, 18.7, 28.9, 57.4, 61.7, 118.2, 121.6, 122.0, 122.3, 125.2, 128.7, 134.7, 135.2, 135.8, 153.2, 169.2. — IR: ν = 3296, 3205, 1722, 1697, 1628, 1604, 1565, 1340, 1252, 1194, 1141, 1074, 1028, 846. — C₁₉H₂₂N₄O₅ (355.43): calcd. C 59.06; H 5.74; N 14.50; found C 59.27, H 6.09, 14.83.

(S)-N-(1-Hydroxy-3-methylbutan-2-yl)-2-methyl-2-(3-phenylureido)propanamide (20g). According to the general procedure product **20g** was yielded as white solid (0.630 g, 2.04 mmol, 100%) starting from acid **19c** (0.500 g, 2.25 mmol) and coupled with L-valinol.

$R_f = 0.25$ (DCM/MeOH 95:5) — m.p. 135–136 °C — $[\alpha]_D^{20} = -38.27$ ($c = 0.1$, CHCl₃) — ¹H NMR (400 MHz, CDCl₃, 25 °C): δ = 0.86 (d, 3H, $J = 6.8$ Hz), 0.89 (d, 3H, $J = 6.7$ Hz), 1.52 (s, 3H), 1.53 (s, 3H), 1.70 (m, 1H), 3.39 (t, 1H, $J = 10.2$ Hz), 3.70 (m, 2H), 3.98 (bs, 1H), 6.43 (s, 1H), 6.86 (d, 1H, $J = 9.8$ Hz), 6.94 (t, 1H, $J = 7.2$ Hz), 7.15 (t, 2H, 7.6 Hz), 7.28 (d, 2H, 7.7 Hz), 8.09 (s, 1H). — ¹³C NMR (100.6 MHz, CHCl₃, 25 °C): δ = 19.2, 19.7, 24.7, 26.9, 29.1, 56.8, 57.9, 64.2, 120.1, 123.0, 128.7, 138.7, 156.1, 177.4. — IR: ν = 3358, 2724, 1649, 1578, 1542, 1310, 1150, 1133, 1087, 965. — C₁₆H₂₅N₃O₃ (307.39): calcd. C 62.52; H 8.20; N 13.67; found C 62.22, H 8.06, N 14.01.

(R)-N-(1-Hydroxybutan-2-yl)-2-methyl-2-(3-phenylureido)propanamide (20h). According to the general procedure product **20h** was yielded as white solid (0.630 g, 2.04 mmol, 100%) starting

from acid **19c** (0.500 g, 2.25 mmol) and coupled with (*R*)-2-aminobutan-1-ol.

$R_f = 0.27$ (DCM/MeOH 95:5). — m.p. 137–138 °C — $[\alpha]_D^{20} = +39.99$ ($c = 0.1$, CHCl₃) — **¹H NMR** (400 MHz, CD₃OD, 25 °C): $\delta = 0.94$ (t, 3H, $J = 7.6$ Hz), 1.46 (m, 1H), 1.50 (s, 6H), 1.62 (m, 1H), 3.52 (d, 2H, $J = 5.4$ Hz), 3.81 (m, 1H), 6.97 (t, 1H, $J = 7.3$ Hz), 7.23 (m, 2H), 7.33 (dd, 2H, $J = 8.5$, 1.0 Hz). — **¹³C NMR** (100.6 MHz, CHCl₃, 25 °C): $\delta = 10.6$, 23.4, 24.8, 26.9, 53.9, 56.7, 65.6, 120.0, 123.0, 128.7, 138.7, 156.0, 177.4. — **IR**: $\nu = 3382$, 3271, 3133, 2724, 1648, 1598, 1542, 1494, 1312, 1253, 1220, 1168, 1062, 845. — C₁₅H₂₃N₃O₃ (293.36): calcd. C 61.41; H 7.90; N 14.32; found C 61.22, H 8.01, N 13.97.

(*S*)-*N*-(1-Hydroxy-3-methylbutan-2-yl)-3-(3-

phenylureido)propanamide (20i). According to the general procedure product **20i** was yielded as white solid (0.569 g, 1.94 mmol, 89%) starting from the acid **19d** (0.500 g, 2.4 mmol) and coupled with L-valinol.

$R_f = 0.22$ (DCM/MeOH 95:5). — m.p. 121–122 °C — $[\alpha]_D^{20} = -31.01$ ($c = 0.1$, CHCl₃) — **¹H NMR** (400 MHz, CDCl₃, 25 °C): $\delta = 0.89$ (d, 3H, $J = 6.8$ Hz), 0.91 (d, 3H, $J = 6.8$ Hz), 1.83 (m, 1H), 2.57 (m, 2H), 2.90 (bs, 1H), 3.47–3.59 (m, 3H), 3.67 (dd, 1H, $J = 11.6$, 3.2 Hz), 3.75 (m, 1H), 6.85 (d, 1H, $J = 8.5$ Hz), 6.98 (m, 1H), 7.21 (m, 2H), 7.28 (m, 1H), 7.44 (m, 1H), 7.55 (m, 1H), 7.86 (bs, 1H). — **¹³C NMR** (100.6 MHz, CDCl₃, 25 °C): $\delta = 18.9$, 19.4, 29.1, 36.5, 37.2, 57.4, 63.3, 119.8, 123.1, 128.9, 138.7, 156.9, 173.4. — **IR**: $\nu = 3337$, 3243, 3087, 2478, 2419, 1670, 1632, 1560, 1503, 1354, 1295, 1260, 1141, 1117, 1063, 1029, 970, 760. — C₁₅H₂₃N₃O₃ (293.36): calcd. C 61.41; H 7.90; N 14.32; found C 61.21, H 8.02, N 14.72.

(*S*)-*N*-(1-Hydroxy-3-phenylpropan-2-yl)-3-(3-

phenylureido)propanamide (20j). According to the general procedure product **20j** was yielded as white solid (0.802 g, 2.35 mmol, 98%) starting from acid **19d** (0.500 g, 2.4 mmol) and coupled with (*S*)-2-amino-3-phenylpropan-1-ol.

$R_f = 0.30$ (DCM/MeOH 95:5). — m.p. 131–132 °C — $[\alpha]_D^{20} = -34.68$ ($c = 0.1$, CHCl₃) — **¹H NMR** (400 MHz, CD₃OD, 25 °C): $\delta = 2.38$ (t, 2H, $J = 6.4$ Hz), 2.71 (dd, 1H, $J = 13.8$, 8.1), 2.90 (dd, 1H, $J = 13.8$, 6.2 Hz), 3.38 (m, 2H), 3.53 (m, 2H), 4.12 (m, 1H), 6.97 (m, 1H), 7.15 (m, 1H), 7.21–7.27 (m, 6H), 7.33 (m, 2H). — **¹³C NMR** (100.6 MHz, CD₃OD, 25 °C): $\delta = 35.9$, 36.1, 36.6, 52.8, 62.9, 118.8, 122.1, 125.9, 126.9, 127.9, 128.4, 128.9, 138.4, 139.5, 156.8, 172.5. — **IR**: $\nu = 3320$, 2724, 2453, 1829, 1738, 1625, 1545, 1308, 1263, 1156, 1071, 1036. — C₁₉H₂₃N₃O₃ (341.40): calcd. C 66.84; H 6.79; N 12.31; found C 67.01, H 6.46, N 12.37.

(*R*)-*N*-(1-Hydroxybutan-2-yl)-3-(3-phenylureido)propanamide (20k)

According to the general procedure product **20k** was yielded as white solid (0.604 g, 2.16 mmol, 99%) starting from acid **19d** (0.500 g, 2.4 mmol) and coupled with (*R*)-2-aminobutan-1-ol.

$R_f = 0.23$ (DCM/MeOH 94:6). — m.p. 131–132 °C — $[\alpha]_D^{20} = +32.01$ ($c = 0.1$, CHCl₃) — **¹H NMR** (400 MHz, CD₃OD, 25 °C): $\delta = 0.93$ (t, 3H, $J = 7.4$ Hz), 1.42 (m, 1H), 1.63 (m, 1H), 2.46 (m, 2H), 3.43–3.52 (m, 4H), 3.80 (m, 1H), 6.97 (m, 1H), 7.23 (m, 2H), 7.33 (m, 2H). — **¹³C NMR** (100.6 MHz, CD₃OD, 25 °C): $\delta = 18.6$, 23.9, 36.5, 37.3, 53.9, 64.8, 119.8, 123.0, 128.9, 138.9, 157.0, 173.3. — **IR**: $\nu = 3327$, 3265, 2724, 1738, 1647, 1557, 1307, 1154, 1070. — C₁₄H₂₁N₃O₃ (279.33): calcd. C 60.20; H 7.58; N 15.04; found C 60.42, H 7.59, N 14.79.

(*R*)-*N*-(2-Hydroxy-1-phenylethyl)-3-(3-phenylureido)propanamide

(20l). According to the general procedure product **20l** was yielded as white solid (0.505 g, 1.54 mmol, 64%) starting from acid **19d** (0.500 g, 2.4 mmol) and coupled with (*R*)-2-amino-2-phenylethanol.

$R_f = 0.31$ (DCM/MeOH 95:5). — m.p. 119–120 °C — $[\alpha]_D^{20} = -37.23$ ($c = 0.1$, CHCl₃) — **¹H NMR** (400 MHz, CD₃OD, 25 °C): $\delta = 2.53$ (m, 2H), 3.47 (t, 2H, $J = 6.5$ Hz), 3.77 (dd, 1H, $J = 11.2$, 7.7 Hz), 3.75 (dd, 1H, $J = 11.2$, 5.3 Hz), 5.01 (dd, 1H, $J = 7.7$, 5.3 Hz), 6.97 (tt, 1H, $J = 7.3$, 1.2 Hz), 7.20–7.35 (m, 9H). — **¹³C NMR** (100.6 MHz, CD₃OD, 25 °C): $\delta = 35.9$, 36.0, 55.6, 64.9, 118.8, 122.0, 126.6, 127.0, 128.1, 128.4, 139.5, 139.9, 156.8, 172.5. — **IR**: $\nu = 3382$, 3308, 2462, 2364, 1644, 1598, 1544, 1313, 1243,

1153, 1125, 1078, 1056, 905. — C₁₈H₂₁N₃O₃ (327.38): calcd. C 66.04; H 6.47; N 12.84; found C 65.89, H 6.75, N 12.56.

(*S*)-*N*-(1-Hydroxy-3-phenylpropan-2-yl)-3-(3-(2-

nitrophenyl)ureido)propanamide (20m). According to the general procedure product **20m** was yielded as yellow solid (0.211 g, 0.546 mmol, 46%) starting from acid **19e** (0.300 g, 1.18 mmol) and coupled with (*S*)-2-amino-3-phenylpropan-1-ol.

$R_f = 0.31$ (DCM/MeOH 95:5). — m.p. 146–147 °C — $[\alpha]_D^{20} = -43.40$ ($c = 0.1$, CHCl₃) — **¹H NMR** (400 MHz, CD₃OD, 25 °C): $\delta = 2.40$ (t, 2H, $J = 6.6$ Hz), 2.72 (dd, 1H, $J = 13.7$, 8.3), 2.90 (dd, 1H, $J = 13.7$, 6.1 Hz), 3.41 (m, 2H), 3.51 (dd, 1H, $J = 11.1$, 5.6 Hz), 3.56 (dd, 1H, $J = 10.6$, 5.1 Hz), 4.14 (m, 1H), 7.13 (m, 2H), 7.23 (m, 4H), 7.61 (ddd, 1H, $J = 8.7$, 7.2, 1.6), 8.13 (dd, 1H, $J = 8.4$, 1.6 Hz), 8.35 (dd, 1H, $J = 8.6$, 1.2 Hz). — **¹³C NMR** (100.6 MHz, CD₃OD, 25 °C): $\delta = 35.9$, 36.2, 36.6, 52.8, 62.8, 121.4, 122.1, 125.1, 125.9, 127.8, 128.9, 134.6, 135.7, 137.1, 138.4, 155.4, 172.2. — **IR**: $\nu = 3371$, 3329, 3282, 2368, 1676, 1649, 1585, 1556, 1155, 1116, 1082, 960, 840. — C₁₉H₂₂N₄O₅ (355.43): calcd. C 59.06; H 5.74; N 14.50; found C 59.23, H 6.00, 14.76.

(*S*)-3-(3-Cyclohexylureido)-*N*-(1-hydroxy-3-methylbutan-2-

yl)propanamide (20n). According to the general procedure product **20n** was yielded as white solid (0.688 g, 2.19 mmol, 99%) starting from acid **19f** (0.500 g, 2.3 mmol) and coupled with L-valinol.

$R_f = 0.44$ (DCM/MeOH 95:5). — m.p. 140–141 °C — $[\alpha]_D^{20} = -30.12$ ($c = 0.1$, CHCl₃) — **¹H NMR** (400 MHz, CD₃OD, 25 °C): $\delta = 0.91$ (d, 3H, $J = 6.7$ Hz), 0.94 (d, 3H, $J = 6.7$ Hz), 1.17 (m, 3H), 1.34 (m, 3H), 1.60 (dt, 1H, $J = 12.6$, 3.8 Hz), 1.72 (dt, 1H, $J = 13.3$, 3.8 Hz), 1.85 (m, 3H), 2.42 (m, 2H), 3.39 (m, 2H), 3.53 (dd, 1H, $J = 11.4$, 6.6 Hz), 3.61 (dd, 1H, $J = 11.3$, 4.4 Hz), 3.71 (m, 1H). — **¹³C NMR** (100.6 MHz, CD₃OD, 25 °C): $\delta = 17.4$, 18.6, 24.6, 25.3, 28.6, 33.3, 36.1, 36.5, 56.6, 61.9, 158.9, 172.9. — **IR**: $\nu = 3312$, 3278, 2409, 1623, 1578, 1545, 1345, 1214, 1123, 1076, 965. — C₁₅H₂₉N₃O₃ (299.41): calcd. C 60.17; H 9.76; N 14.03; found C 59.89, H 10.09, 14.33.

General procedure for the synthesis of products 1–16: Peptide **20** (1.0 equiv.) was dissolved in THF (0.1 M solution) and cooled at –78 °C; then DAST (2.2 equiv.) was added dropwise and the reaction stirred at the same temperature for 90 minutes. The mixture was filtered and the solvent evaporated under reduced pressure. The product was purified by flash chromatography eluting with MeOH (gradient from 1 to 5%) in DCM.

(*S*)-1-(3-(4-Isopropyl-4,5-dihydrooxazol-2-yl)phenyl)-3-phenylurea (1).

According to the general procedure product **1** was yielded as white solid (0.458 g, 1.42 mmol, 91%) starting from precursor **20a** (0.530 g, 1.55 mmol).

$R_f = 0.49$ (DCM/MeOH 95:5). — m.p. 138–139 °C — $[\alpha]_D^{20} = -35.05$ ($c = 0.1$, CHCl₃) — **¹H NMR** (400 MHz, CD₂Cl₂, 25 °C): $\delta = 0.92$ (d, 3H, $J = 6.8$ Hz), 1.01 (d, 3H, $J = 6.7$ Hz), 1.84 (m, 1H), 4.09 (ddd, 1H, $J = 9.5$, 8.2, 6.4 Hz), 4.16 (t, 1H, 8.2 Hz), 4.43 (dd, 1H, $J = 9.5$, 8.3 Hz), 7.10 (m, 1H), 7.14 (bs, 1H), 7.25 (bs, 1H), 7.28–7.37 (m, 5H), 7.50 (ddd, 1H, $J = 8.0$, 2.1, 0.9 Hz), 7.60 (dt, 1H, $J = 7.7$, 1.1 Hz), 7.95 (t, 1H, $J = 1.7$ Hz). — **¹³C NMR** (100.6 MHz, CDCl₃, 25 °C): $\delta = 17.6$, 18.8, 32.4, 70.6, 71.2, 119.4, 120.8, 123.2, 123.6, 123.9, 128.9, 129.1, 129.3, 138.0, 138.8, 139.0, 153.6, 165.0. — **IR**: $\nu = 3319$, 2725, 1743, 1646, 1595, 1567, 1309, 1262, 1155, 1069, 801. — C₁₉H₂₁N₃O₂ (323.39): calcd. C 70.57; H 6.55, N 12.99; found C 70.19, H 6.41, N 12.83.

(*R*)-1-(3-(4-ethyl-4,5-dihydrooxazol-2-yl)phenyl)-3-phenylurea (2).

According to the general procedure product **2** was yielded as white solid (0.370 g, 1.20 mmol, 78%) starting from precursor **20b** (0.500 g, 1.53 mmol).

$R_f = 0.46$ (DCM/MeOH 95:5). — m.p. 147–148 °C — $[\alpha]_D^{20} = +43.30$ ($c = 0.1$, CHCl₃) — **¹H NMR** (400 MHz, CD₃OD, 25 °C): $\delta = 0.99$ (t, 3H, $J = 7.3$ Hz), 1.63 (m, 1H), 1.74 (m, 1H), 4.14 (t, 1H, $J = 7.7$ Hz), 4.24 (m, 1H), 4.54 (dd, 1H, $J = 9.4$, 8.2 Hz), 7.02 (m, 1H), 7.29 (m, 2H), 7.37 (t, 1H, $J = 8.2$ Hz), 7.43 (dd, 2H, $J = 8.7$, 1.1 Hz), 7.58 (dt, 1H, $J = 7.7$, 1.3 Hz), 7.68 (ddd, 1H, $J = 8.1$, 2.3, 1.0 Hz), 7.96 (t, 1H, $J = 2.0$ Hz). — **¹³C NMR** (100.6

MHz, CD₃OD, 25 °C): δ = 8.52, 28.0, 67.1, 72.0, 118.4, 119.0, 122.1, 122.6, 127.8, 128.5, 128.7, 138.9, 139.6, 153.8, 164.6. — **IR**: ν = 3309, 3281, 1644, 1612, 1592, 1572, 1448, 1311, 1298, 1237, 1168, 1080, 1059, 973, 926. — C₁₈H₁₉N₃O₂ (309.36): calcd. C 69.98; H 6.19, N 13.58; found C 70.01, H 6.15, N 13.54.

(S)-1-(3-(4-Benzyl-4,5-dihydrooxazol-2-yl)phenyl)-3-phenylurea (3).

According to the general procedure product **3** was yielded as white solid (0.518 g, 1.39 mmol, 78%) starting from precursor **20c** (0.693 g, 1.78 mmol).

R_f = 0.52 (DCM/MeOH 95:5). — m.p. 106–107 °C — $[\alpha]_D^{20}$ = -37.89 (c = 0.1, CHCl₃) — **¹H NMR** (400 MHz, CHCl₃, 25 °C): δ = 2.64 (dd, 1H, J = 13.7, 9.0 Hz), 3.12 (dd, 1H, J = 13.7, 5.1 Hz), 4.02 (t, 1H, J = 7.8 Hz), 4.22 (t, 1H, J = 8.8 Hz), 4.47 (m, 1H), 6.95 (t, 1H, J = 7.1 Hz), 7.11–7.27 (m, 11H), 7.54 (d, 1H, J = 7.1 Hz), 7.94 (d, 2H, J = 8.1 Hz), 8.04 (s, 1H). — **¹³C NMR** (100.6 MHz, CDCl₃, 25 °C): δ = 41.8, 67.6, 72.0, 119.8, 120.5, 123.0, 123.1, 123.6, 126.6, 128.1, 128.6, 128.9, 129.0, 129.1, 137.8, 138.2, 138.7, 154.0, 164.4. — **IR**: ν = 3353, 2724, 2360, 1649, 1597, 1555, 1310, 1264, 1201, 1154, 1074, 896, 845. — C₂₃H₂₁N₃O₂ (371.43): calcd. C 74.37; H 5.70, N 11.31; found C 77.37, H 5.68, N 10.95.

(S)-1-(3-(4-tert-Butyl-4,5-dihydrooxazol-2-yl)phenyl)-3-phenylurea (4).

According to the general procedure product **4** was yielded as white solid (0.436 g, 1.29 mmol, 83%) starting from precursor **20d** (0.552 g, 1.55 mmol).

R_f = 0.48 (DCM/MeOH 95:5). — m.p. 170–171 °C — $[\alpha]_D^{20}$ = -47.13 (c = 0.1, CHCl₃) — **¹H NMR** (400 MHz, CD₃OD, 25 °C): δ = 1.02 (s, 9H), 3.63 (dd, 1H, J = 11.5, 8.9 Hz), 3.88 (dd, 1H, J = 11.5, 3.4 Hz), 4.04 (dd, 1H, J = 8.9, 3.4 Hz), 7.03 (t, 1H, J = 7.4 Hz), 7.30 (dd, 2H, J = 8.4, 7.4 Hz), 7.40 (t, 1H, J = 7.7 Hz), 7.44 (m, 2H), 7.48 (ddd, 1H, J = 7.7, 1.7, 1.1 Hz), 7.59 (ddd, 1H, J = 8.2, 2.2, 1.1 Hz), 7.82 (t, 1H, J = 1.7 Hz). — **¹³C NMR** (100.6 MHz, CDCl₃, 25 °C): δ = 25.8, 33.9, 68.8, 75.9, 119.8, 120.6, 123.0, 123.1, 123.6, 128.3, 129.0, 138.1, 138.6, 154.0, 163.7. — **IR**: ν = 3352, 2724, 2360, 1740, 1647, 1596, 1560, 1309, 1264, 1204, 1154, 1073, 897, 799. — C₂₀H₂₃N₃O₂ (337.42): calcd. C 71.19; H 6.87, N 12.45; found C 71.44, H 7.10, N 12.47.

(R)-1-Phenyl-3-(3-(4-phenyl-4,5-dihydrooxazol-2-yl)phenyl)urea (5).

According to the general procedure product **5** was yielded as white solid (0.103 g, 0.29 mmol, 30%) starting from precursor **20e** (0.400 g, 1.06 mmol).

R_f = 0.45 (DCM/MeOH 95:5). — m.p. 134–135 °C — $[\alpha]_D^{20}$ = -51.78 (c = 0.1, CHCl₃) — **¹H NMR** (400 MHz, CDCl₃, 25 °C): δ = 4.25 (t, 1H, J = 8.3 Hz), 4.90 (dd, 1H, J = 10.1, 8.3 Hz), 5.45 (dd, 1H, J = 10.1, 8.3 Hz), 6.98 (t, 1H, J = 7.3 Hz), 7.24–7.31 (m, 3H), 7.34–7.41 (m, 5H), 7.55 (dd, 2H, J = 8.7, 1.1 Hz), 7.65 (dt, 1H, J = 7.7, 1.3 Hz), 7.73 (ddd, 1H, J = 8.2, 2.3, 1.1 Hz), 8.23 (t, 1H, J = 1.9 Hz), 8.36 (s, 1H), 8.52 (s, 1H). — **¹³C NMR** (100.6 MHz, CDCl₃, 25 °C): δ = 69.5, 74.9, 118.2, 118.5, 118.6, 121.5, 121.6, 121.9, 122.1, 126.7, 127.3, 128.1, 128.5, 128.7, 128.9, 139.9, 140.4, 142.9, 152.5, 164.3. — **IR**: ν = 3321, 3278, 2725, 1709, 1656, 1611, 1561, 1311, 1223, 1189, 1063, 970, 840. — C₂₂H₁₉N₃O₂ (357.41): calcd. C 73.93; H 5.36, N 11.76; found C 73.57, H 5.63, N 11.46.

(S)-1-(3-(4-Isopropyl-4,5-dihydrooxazol-2-yl)phenyl)-3-(2-nitrophenyl)urea (6).

According to the general procedure product **6** was yielded as yellow solid (0.441 g, 1.20 mmol, 82%) starting from precursor **20f** (0.565 g, 1.46 mmol).

R_f = 0.38 (DCM/MeOH 95:5). — m.p. 166–167 °C — $[\alpha]_D^{20}$ = -49.37 (c = 0.1, CHCl₃) — **¹H NMR** (400 MHz, CD₂Cl₂, 25 °C): δ = (d, 3H, J = 6.7 Hz), 1.05 (d, 3H, J = 6.7 Hz), 1.84 (m, 1H), 4.07–4.18 (m, 2H), 4.45 (dd, 1H, J = 9.2, 7.8 Hz), 7.10 (bs, 1H), 7.15 (ddd, 1H, J = 8.4, 7.2, 1.3 Hz), 7.43 (t, 1H, J = 7.7 Hz), 7.64 (ddd, 1H, J = 7.9, 2.1, 1.0 Hz), 7.68 (ddd, 1H, J = 8.7, 7.1, 1.6 Hz), 7.72 (dt, 1H, J = 7.7, 1.2 Hz), 8.04 (t, 1H, J = 2.0 Hz), 8.22 (dd, 1H, J = 8.6, 1.6 Hz), 8.68 (dd, 1H, J = 8.7, 1.1 Hz), 9.94 (bs, 1H). — **¹³C NMR** (100.6 MHz, CH₂Cl₂, 25 °C): δ = 17.8, 18.6, 32.8, 70.3, 72.5, 119.7, 121.9, 122.1, 122.9, 123.4, 125.5, 128.8, 129.1, 135.4, 136.0, 136.7, 138.4, 151.8, 163.1. — **IR**: ν = 3339, 3281, 2724, 1650, 1591, 1557,

1309, 1278, 1155, 1066, 823. — C₁₉H₂₀N₄O₄ (368.39): calcd. C 61.95; H 5.47, N 15.21; found C 61.71, H 5.84, N 13.47.

(S)-1-(2-(4-Isopropyl-4,5-dihydrooxazol-2-yl)propan-2-yl)-3-phenylurea (7).

According to the general procedure product **7** was yielded as white solid (0.501 g, 1.73 mmol, 84%) starting from precursor **20g** (0.635 g, 2.06 mmol).

R_f = 0.50 (DCM/MeOH 95:5). — m.p. 189–190 °C — $[\alpha]_D^{20}$ = -43.12 (c = 0.1, CHCl₃) — **¹H NMR** (400 MHz, CD₃OD, 25 °C): δ = 0.89 (d, 3H, J = 6.7 Hz), 0.95 (d, 3H, J = 6.8 Hz), 1.56 (s, 3H), 1.59 (s, 3H), 1.82 (m, 1H), 4.00 (ddd, 1H, J = 9.8, 7.2, 5.5 Hz), 4.12 (dd, 1H, J = 8.6, 7.2 Hz), 4.32 (dd, 1H, J = 9.8, 8.6 Hz), 6.96 (m, 1H), 7.23 (dd, 2H, J = 8.6, 7.5 Hz), 7.31 (dd, 2H, J = 8.6, 1.2). — **¹³C NMR** (100.6 MHz, CD₃OD, 25 °C): δ = 16.4, 17.5, 25.5, 25.7, 31.9, 51.5, 70.0, 71.2, 118.6, 121.9, 128.9, 139.4, 155.5, 172.2. — **IR**: ν = 3338, 2725, 1646, 1600, 1557, 1543, 1310, 1264, 1152, 1071, 800. — C₁₆H₂₃N₃O₂ (289.37): calcd. C 66.41; H 8.01, N 14.52; found C 66.53, H 8.11, 14.77.

(S)-1-(2-(4-Ethyl-4,5-dihydrooxazol-2-yl)propan-2-yl)-3-phenylurea (8).

According to the general procedure product **8** was yielded as white solid (0.441 g, 1.60 mmol, 74%) starting from precursor **20h** (0.636 g, 2.17 mmol).

R_f = 0.49 (DCM/MeOH 95:5). — m.p. 122–123 °C — $[\alpha]_D^{20}$ = +40.82 (c = 0.1, CHCl₃) — **¹H NMR** (400 MHz, CD₃OD, 25 °C): δ = 0.94 (t, 3H, J = 7.3 Hz), 1.55 (s, 3H), 1.56 (m, 1H), 1.57 (s, 3H), 1.66 (m, 1H), 4.01 (t, 1H, J = 7.6 Hz), 4.08 (m, 1H), 4.39 (dd, 1H, J = 9.0, 7.8 Hz), 6.96 (t, 1H, J = 7.3 Hz), 7.23 (t, 2H, J = 7.9 Hz), 7.30 (dd, 2H, J = 8.8, 1.2 Hz). — **¹³C NMR** (100.6 MHz, CD₃OD, 25 °C): δ = 8.3, 25.5, 25.6, 27.6, 51.3, 66.8, 72.3, 118.6, 122.0, 128.3, 139.3, 155.4, 172.2. — **IR**: ν = 3321, 2725, 1661, 1641, 1596, 1587, 1500, 1302, 1250, 1218, 1132, 1082, 1068, 979, 955, 924, 843. — C₁₅H₂₁N₃O₂ (275.35): calcd. C 65.43; H 7.69, N 15.26; found C 65.57, H 7.66, N 15.37.

(S)-1-(2-(4-Isopropyl-4,5-dihydrooxazol-2-yl)ethyl)-3-phenylurea (9).

According to the general procedure product **9** was yielded as white solid (0.519 g, 1.88 mmol, 99%) starting from precursor **20i** (0.560 g, 1.91 mmol).

R_f = 0.59 (DCM/MeOH 95:5). — m.p. 81–81 °C — $[\alpha]_D^{20}$ = -29.80 (c = 0.1, CHCl₃) — **¹H NMR** (400 MHz, CD₃OD, 25 °C): δ = 0.89 (d, 3H, J = 6.8 Hz), 0.94 (d, 3H, J = 6.7 Hz), 1.74 (m, 1H), 2.52 (m, 2H), 3.49 (m, 2H), 3.91 (m, 1H), 4.07 (t, 1H, J = 7.9 Hz), 4.31 (dd, 1H, J = 9.8, 8.7 Hz), 6.97 (m, 1H), 7.24 (m, 2H), 7.33 (dd, 2H, J = 8.7, 1.2 Hz). — **¹³C NMR** (100.6 MHz, CD₃OD, 25 °C): δ = 17.4, 18.6, 28.6, 36.1, 36.2, 56.6, 61.8, 118.8, 122, 128.4, 139.5, 156.8, 172.8. — **IR**: ν = 3205, 2728, 1694, 1639, 1594, 1527, 1380, 1353, 1168, 1077, 1029, 920, 832. — C₁₅H₂₁N₃O₂ (273.35): calcd. C 65.43; H 7.69; N 15.26; found C 65.61, H 7.99, 14.61.

(S)-1-(2-(4-Benzyl-4,5-dihydrooxazol-2-yl)ethyl)-3-phenylurea (10).

According to the general procedure product **10** was yielded as pale yellow solid (0.175 g, 0.541 mmol, 53%) starting from precursor **20j** (0.350 g, 1.03 mmol).

R_f = 0.51 (DCM/MeOH 95:5). — m.p. 130–131 °C — $[\alpha]_D^{20}$ = -44.65 (c = 0.1, CHCl₃) — **¹H NMR** (400 MHz, CHCl₃, 25 °C): δ = 2.44 (t, 2H, J = 5.8 Hz), 2.64 (dd, 1H, J = 13.7, 7.8 Hz), 2.96 (dd, 1H, J = 13.7, 5.6 Hz), 3.43–3.62 (m, 2H), 3.98 (t, 1H, J = 7.4 Hz), 4.20 (t, 1H, 8.4 Hz), 4.29 (m, 1H), 6.06 (bs, 1H), 7.03 (t, 1H, J = 7.3 Hz), 7.13 (m, 2H), 7.16–7.40 (m, 8H), 7.63 (bs, 1H). — **¹³C NMR** (100.6 MHz, CDCl₃, 25 °C): δ = 28.8, 36.6, 41.6, 66.7, 71.9, 120.5, 123.3, 126.6, 128.6, 129.1, 129.2, 137.7, 139.0, 156.2, 167.4. — **IR**: ν = 3331, 2724, 1679, 1632, 1595, 1565, 1497, 1444, 1349, 1311, 1242, 1191, 1084, 975, 924. — C₁₉H₂₁N₃O₂ (323.39): calcd. C 70.57; H 6.55; N 12.99; found C 70.78, H 6.32, N 13.04.

(R)-1-(2-(4-Ethyl-4,5-dihydrooxazol-2-yl)ethyl)-3-phenylurea (11).

According to the general procedure product **11** was yielded as pale yellow solid (0.410 g, 1.57 mmol, 77%) starting from precursor **20k** (0.570 g, 2.04 mmol).

R_f = 0.57 (DCM/MeOH 95:5). — m.p. 68–69 °C — $[\alpha]_D^{20}$ = +29.07 (c = 0.1, CHCl₃) — **¹H NMR** (400 MHz, CHCl₃, 25 °C): δ = 0.91 (t, 3H, J =

7.3 Hz), 1.56 (m, 1H), 1.67 (m, 1H), 2.69 (t, 1H, $J = 5.6$ Hz), 3.57 (m, 2H), 4.06-4.20 (m, 2H), 4.63 (t, 1H, $J = 8.8$ Hz), 6.38 (bs, 1H), 7.02 (t, 1H, $J = 7.7$ Hz), 7.25 (m, 2H), 7.39 (d, 2H, $J = 7.3$ Hz), 7.75 (bs, 1H). — ^{13}C NMR (100.6 MHz, CDCl_3 , 25 °C): $\delta = 9.8, 24.0, 36.5, 37.3, 53.6, 64.6, 119.6, 122.8, 128.9, 139.2, 156.8, 173.0$. — IR: $\nu = 3321, 2725, 1640, 1556, 1309, 1243, 1156, 1070$. — $\text{C}_{14}\text{H}_{19}\text{N}_3\text{O}_2$ (261.32): calcd. C 64.35; H 7.33; N 16.08; found C 64.44, H 7.43, N 15.41.

(R)-1-Phenyl-3-(2-(4-phenyl-4,5-dihydrooxazol-2-yl)ethyl)urea (12). According to the general procedure product **12** was yielded white solid (0.257 g, 0.83 mmol, 77%) starting from precursor **20l** (0.500 g, 1.54 mmol).

$R_f = 0.59$ (DCM/MeOH 95:5). — m.p. 122-123 °C — $[\alpha]_D^{20} = +38.08$ ($c = 0.1$, CHCl_3) — ^1H NMR (400 MHz, CHCl_3 , 25 °C): $\delta = 2.51$ (t, 2H, $J = 5.8$ Hz), 3.54 (m, 2H), 4.06 (t, 1H, $J = 8.3$ Hz), 4.56 (dd, 1H, $J = 10.1, 8.6$ Hz), 5.09 (t, 1H, $J = 9.2$ Hz), 6.18 (t, 1H, $J = 6.0$ Hz), 6.97 (m, 1H), 7.13-7.36 (m, 10H). — ^{13}C NMR (100.6 MHz, CDCl_3 , 25 °C): $\delta = 28.9, 36.6, 67.7, 69.4, 120.1, 122.9, 127.8, 128.8, 129.0, 139.1, 141.8, 156.4, 171.8$. — IR: $\nu = 3310, 2726, 1678, 1620, 1567, 1541, 1310, 1245, 1180, 1076, 978, 845$. — $\text{C}_{18}\text{H}_{19}\text{N}_3\text{O}_2$ (309.36): calcd. C 69.88; H 6.12; N 13.58; found C 69.58, H 6.34, N 13.89.

(S)-1-(2-(4-Benzyl-4,5-dihydrooxazol-2-yl)ethyl)-3-(2-nitrophenyl)urea (13). According to the general procedure product **13** was yielded as yellow solid (0.101 g, 0.274 mmol, 50%) starting from precursor **20m** (0.210 g, 0.543 mmol).

$R_f = 0.34$ (DCM/MeOH 95:5). — m.p. 154-155 °C — $[\alpha]_D^{20} = -42.12$ ($c = 0.1$, CHCl_3) — ^1H NMR (400 MHz, CDCl_3 , 25 °C): $\delta = 2.56$ (t, 2H, $J = 5.7$ Hz), 2.78 (dd, 1H, $J = 13.7, 7.9$ Hz), 3.08 (dd, 1H, $J = 13.7, 5.4$ Hz), 3.61 (m, 2H), 4.10 (dd, 1H, $J = 8.3, 7.4$ Hz), 4.33 (t, 1H, $J = 8.9$ Hz), 4.49 (m, 1H), 6.17 (bs, 1H), 7.04 (m, 1H), 7.20-7.35 (m, 5H), 7.58 (ddd, 1H, $J = 8.7, 7.3, 1.6$ Hz), 8.16 (dd, 1H, $J = 8.4, 1.5$ Hz), 8.58 (d, 1H, $J = 8.6$ Hz), 9.72 (s, 1H). — ^{13}C NMR (100.6 MHz, CDCl_3 , 25 °C): $\delta = 28.1, 36.6, 41.5, 66.6, 71.9, 121.3, 121.5, 125.7, 126.7, 128.6, 129.3, 134.7, 135.8, 137.0, 137.4, 153.9, 172.2$. — IR: $\nu = 3353, 2724, 1651, 1613, 1543, 1309, 1264, 1140, 1104, 794$. — $\text{C}_{19}\text{H}_{20}\text{N}_4\text{O}_4$ (368.38): calcd. C 61.95; H 5.47; N 15.21; found C 61.66, H 5.78, N 14.99.

(S)-1-Cyclohexyl-3-(2-(4-isopropyl-4,5-dihydrooxazol-2-yl)ethyl)urea (14). According to the general procedure product **14** was yielded as white solid (0.402 g, 1.42 mmol, 62%) starting from precursor **20n** (0.688 g, 2.30 mmol).

$R_f = 0.54$ (DCM/MeOH 95:5). — m.p. 103-104 °C — $[\alpha]_D^{20} = -39.45$ ($c = 0.1$, CHCl_3) — ^1H NMR (400 MHz, CDCl_3 , 25 °C): $\delta = 0.90$ (d, 3H, $J = 6.8$ Hz), 0.98 (d, 3H, $J = 6.8$ Hz), 1.08-1.39 (m, 6H), 1.59 (dt, 1H, $J = 12.8, 3.8$ Hz), 1.71 (m, 2H), 1.77 (m, 1H), 1.92 (m, 2H), 2.50 (m, 2H), 3.51 (m, 2H), 3.92 (m, 1H), 4.02 (t, 1H, $J = 8.1$ Hz), 4.32 (dd, 1H, $J = 9.5, 8.5$ Hz), 4.61 (d, 1H, $J = 7.5$ Hz), 5.49 (bs, 1H). — ^{13}C NMR (100.6 MHz, CDCl_3 , 25 °C): $\delta = 18.1, 18.7, 24.9, 25.6, 28.6, 32.5, 33.9, 36.6, 49.4, 70.3, 71.3, 157.6, 167.4$. — IR: $\nu = 3351, 3305, 2350, 1669, 1624, 1579, 1532, 1309, 1251, 1167, 1082, 982, 939, 891, 791$. — $\text{C}_{15}\text{H}_{27}\text{N}_3\text{O}_2$ (281.39): calcd. C 64.02; H 9.67; N 14.93; found C 63.89, H 9.90, N 14.79.

4-(Allyloxy)-4-oxo-2-(3-phenylureido)butanoic acid (22a-b). 4-(Allyloxy)-2-amino-4-oxobutanoic acid hydrochloride **21a-b** (1.20 g, 5.72 mmol, 1.0 equiv.) was suspended in 57 mL THF and triethylamine (0.79 mL, 5.72 mmol, 1.0 equiv.) added dropwise. The reaction mixture was vigorously stirred for 30 minutes then phenylisocyanate (0.65 mL, 5.72 mmol, 1.0 equiv.) added and stirred for 3 days at room temperature. The mixture was treated with aq. Et_2O to provide the precipitation of a white powder. The solid was washed with KHSO_4 1M to obtain product **22a** and **22b** as fine white powder (*R*-enantiomer: 1.394 g, 4.77 mmol, 83%. *S*-enantiomer: 1.407 g, 4.81 mmol, 84%).

$R_f = 0.28$ (DCM/MeOH 95:5) — m.p. 186-187 °C — ^1H NMR (400 MHz, CDCl_3 , 25 °C): $\delta = 2.86$ (bs, 2H), 4.54 (bs, 2H), 4.78 (bs, 1H), 5.19 (d, 1H, $J = 10.4$ Hz), 5.26 (d, 1H, $J = 17.1$ Hz), 5.84 (m, 1H), 6.8 (bs, 1H), 6.96 (t,

1H, $J = 6.8$ Hz), 7.20 (t, 2H, $J = 7.1$ Hz), 7.39 (d, 2H, $J = 7.0$ Hz), 8.46 (bs, 1H), 11.23 (bs, 1H). — ^{13}C NMR (100.6 MHz, CDCl_3 , 25 °C): $\delta = 36.5, 49.9, 65.6, 118.4, 119.4, 122.6, 128.8, 131.8, 139.1, 156.5, 170.9$. — IR: $\nu = 3311, 2738, 2603, 2531, 2496, 1716, 1702, 1596, 1547, 1397, 1172, 1072, 1036, 851, 807$. — $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_5$ (292.29): calcd. C 57.53; H 5.52; N 9.58; found C 57.89, H 5.87, N 9.34.

Allyl 4-oxo-3-(3-phenylureido)-4-(pyrrolidin-1-yl)butanoate (23a-b). 4-(allyloxy)-4-oxo-2-(3-phenylureido)butanoic acid **22a-b** (1.300 g, 4.45 mmol, 1.0 equiv.) and *N,N*-diisopropylethylamine (1.90 mL, 11.1 mmol, 2.5 equiv.) were dissolved in 45 mL DMF and the solution cooled at 0 °C. HBTU (1.3 equiv.) was added and the solution stirred at the same temperature for 30 minutes, then pyrrolidine (0.44 mL, 5.34 mmol, 1.2 equiv.) was added and the reaction mixture stirred at 0 °C for 60 minutes and overnight at room temperature.

The solvent was evaporated under reduced pressure and the mixture separated by flash chromatography eluting with MeOH (gradient from 2 to 6%) in DCM to yield the products **23a-b** as pale yellow oil (*R*-enantiomer: 1.122 g, 3.24 mmol, 73%. *S*-enantiomer: 1.199 g, 3.47 mmol, 78%).

$R_f = 0.28$ (DCM/MeOH 95:5) — ^1H NMR (400 MHz, CDCl_3 , 25 °C): $\delta = 1.88$ (m, 2H), 1.99 (m, 2H), 2.68 (dd, 1H, $J = 15.8, 6.7$ Hz), 2.89 (dd, 1H, $J = 15.8, 7.4$ Hz), 3.42 (m, 2H), 3.67 (m, 1H), 3.78 (m, 1H), 4.59 (t, 1H, $J = 1.3$ Hz), 4.61 (t, 1H, $J = 1.3$ Hz), 5.01 (t, 1H, $J = 7.0$ Hz), 5.20 (ddd, 1H, $J = 10.5, 2.7, 1.2$ Hz), 5.31 (ddd, 1H, $J = 17.2, 3.0, 1.6$ Hz), 5.92 (m, 1H), 6.98 (m, 1H), 7.24 (m, 2H), 7.34 (dd, 2H, $J = 8.8, 1.0$ Hz). — ^{13}C NMR (100.6 MHz, CDCl_3 , 25 °C): $\delta = 23.7, 25.5, 36.6, 46.0, 46.5, 48.2, 65.1, 117.2, 118.8, 122.3, 128.4, 132.1, 139.2, 155.7, 170.2, 170.4$. — IR: $\nu = 2721, 2656, 2512, 2345, 1721, 1678, 1600, 1329, 1178, 1109, 1074, 997, 856$. — $\text{C}_{18}\text{H}_{23}\text{N}_3\text{O}_4$ (345.39): calcd. C 62.59; H 6.71; N 12.17; found C 62.33, H 6.57, N 11.99.

4-Oxo-3-(3-phenylureido)-4-(pyrrolidin-1-yl) butanoic acid (24a-b). Allyl 4-oxo-3-(3-phenylureido)-4-(pyrrolidin-1-yl)butanoate **23a-b** (1.10g, 3.18mmol, 1.0 equiv.) was dissolved in 30 mL DCM and the solution cooled at 0 °C. Pyrrolidine (0.31 mL, 3.82 mmol, 1.2 equiv.), triphenylphosphane (0.149 g, 0.57 mmol, 0.18 equiv.) and tetrakis(triphenylphosphane)palladium(0) (0.147 g, 0.13 mmol, 0.04 equiv.) were added and the reaction mixture stirred for 1 hour at 0 °C. The mixture was poured into AcOEt (200 mL) and extracted with satd. NaHCO_3 solution (5 × 30 mL). The combined organic layers were acidified to pH 2 with 1 M KHSO_4 solution. The acidified aqueous solutions was extracted with DCM (3 × 25 mL) and the combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with 6% MeOH in DCM to yield the product as yellow solid ((*R*)-enantiomer 0.754 g, 2.47 mmol, 77%. (*S*)-enantiomer 0.778 g, 2.55 mmol, 80%).

$R_f = 0.30$ (DCM/MeOH 95:5) — m.p. 168-169 °C — ^1H NMR (400 MHz, CDCl_3 , 25 °C): $\delta = 1.85$ (m, 2H), 1.96 (m, 2H), 2.73 (dd, 1H, $J = 15.7, 6.2$ Hz), 2.84 (dd, 1H, $J = 15.7, 6.1$ Hz), 3.44 (m, 2H), 3.62 (m, 1H), 3.80 (m, 1H), 5.13 (m, 1H), 6.75 (d, 1H, $J = 8.8$ Hz), 6.97 (t, 1H, $J = 7.5$ Hz), 7.21 (t, 2H, $J = 7.5$ Hz), 7.34 (d, 2H, $J = 7.7$ Hz), 8.08 (s, 1H). — ^{13}C NMR (100.6 MHz, CDCl_3 , 25 °C): $\delta = 24.1, 25.9, 37.5, 46.6, 47.1, 48.2, 119.5, 122.7, 128.8, 139.1, 155.4, 170.6, 173.7$. — IR: $\nu = 3347, 3202, 3145, 1728, 1685, 1615, 1553, 1518, 1481, 1312, 1203, 1119, 1046, 997$. — $\text{C}_{15}\text{H}_{19}\text{N}_3\text{O}_4$ (305.33): calcd. C 59.01; H 6.27; N 13.76; found C 59.34, H 5.99, N 13.44.

(S)-N-((S)-1-Hydroxy-3-methylbutan-2-yl)-4-oxo-3-(3-phenylureido)-4-(pyrrolidin-1-yl)butanamide (25a). According to the general procedure product **25a** was yielded as yellow pale oil (0.154 g, 0.39 mmol, 60%) starting from the acid **24a** (0.200 g, 0.65 mmol) and coupled with L-valinol. $R_f = 0.33$ (DCM/MeOH 95:5). — $[\alpha]_D^{20} = -78.04$ ($c = 0.1$, CHCl_3) — ^1H NMR (400 MHz, CD_3OD , 25 °C): $\delta = 0.91$ (d, 3H, $J = 6.8$ Hz), 0.94 (d, 3H, 6.7 Hz), 1.82-1.93 (m, 2H), 2.00 (m, 1H), 2.57 (dd, 1H, $J = 14.4, 7.4$ Hz), 2.72 (dd, 1H, $J = 14.4, 6.7$ Hz), 3.38-3.60 (m, 4H), 3.69 (m, 2H), 3.79 (m, 1H), 5.02 (t, 1H, $J = 7.2$ Hz), 6.98 (m, 1H), 7.24 (m, 2H), 7.33 (m, 2H). — ^{13}C NMR (100.6 MHz, CD_3OD , 25 °C): $\delta = 17.4, 18.6, 23.7, 25.5, 28.5,$

38.4, 45.9, 46.5, 48.8, 56.7, 61.7, 118.8, 122.2, 128.4, 139.2, 155.8, 170.7. — **IR**: ν = 3310, 3259, 2767, 2456, 2412, 1665, 1565, 1508, 1459, 1334, 1300, 1211, 1098, 980, 876. — $\text{C}_{20}\text{H}_{30}\text{N}_4\text{O}_4$ (390.48): calcd. C 61.52; H 7.74; N 14.35; found C 61.66, H 7.60, N 14.53.

(R)-N-((S)-1-Hydroxy-3-methylbutan-2-yl)-4-oxo-3-(3-phenylureido)-4-(pyrrolidin-1-yl)butanamide (25b). According to the general procedure product **25b** was yielded as yellow pale oil (0.144 g, 0.37 mmol, 56%) starting from the acid **24b** (0.200 g, 0.65 mmol) and coupled with L-valinol. R_f = 0.33 (DCM/MeOH 95:5). — $[\alpha]_D^{20}$ = -12.35 (c = 0.1, CHCl_3) — **¹H NMR** (400 MHz, CD_3OD , 25 °C): δ = 0.89 (d, 3H, J = 6.8 Hz), 0.93 (d, 3H, J = 6.7 Hz), 1.80–1.92 (m, 3H), 2.00 (m, 2H), 2.58 (dd, 1H, J = 14.3, 6.8 Hz), 2.73 (dd, 1H, J = 14.3, 7.4 Hz), 3.35–3.63 (m, 4H), 3.70 (m, 2H), 3.82 (m, 1H), 4.99 (t, 1H, J = 7.0 Hz), 6.98 (m, 1H), 7.24 (m, 2H), 7.33 (dd, 2H, J = 8.8, 1.2 Hz). — **¹³C NMR** (100.6 MHz, CD_3OD , 25 °C): δ = 17.3, 18.6, 23.7, 25.5, 28.5, 38.3, 45.9, 46.5, 48.7, 56.7, 61.7, 118.7, 122.2, 128.4, 139.2, 155.8, 170.6, 170.8. — **IR**: ν = 3300, 3256, 2789, 2481, 2426, 1656, 1599, 1548, 1499, 1315, 1224, 1100, 978, 856. — $\text{C}_{20}\text{H}_{30}\text{N}_4\text{O}_4$ (390.48): calcd. C 61.52; H 7.74; N 14.35; found C 61.84, H 7.70, N 14.39.

1-((S)-3-((S)-4-Isopropyl-4,5-dihydrooxazol-2-yl)-1-oxo-1-(pyrrolidin-1-yl)propan-2-yl)-3-phenylurea (15). According to the general procedure, product **15** was yielded as yellow solid (0.083 g, 0.22 mmol, 58%) starting from precursor **25a** (0.150 g, 0.38 mmol).

R_f = 0.43 (DCM/MeOH 95:5). — m.p. 122–123 °C — $[\alpha]_D^{20}$ = -71.70 (c = 0.1, CHCl_3) — **¹H NMR** (400 MHz, CDCl_3 , 25 °C): δ = 0.84 (d, 3H, J = 6.7 Hz), 0.92 (d, 3H, J = 6.7 Hz), 1.66 (m, 1H), 1.87 (m, 2H), 1.96 (m, 2H), 2.68 (dd, 1H, J = 15.2, 6.4 Hz), 2.82 (dd, 1H, J = 15.2, 8.0 Hz), 3.49 (m, 2H), 3.78–3.92 (m, 4H), 4.20 (dd, 1H, J = 9.4, 8.2 Hz), 5.20 (m, 1H), 6.88–6.96 (m, 2H), 7.22 (t, 2H, J = 7.6 Hz), 7.36 (d, 2H, J = 7.6 Hz), 8.26 (s, 1H). — **¹³C NMR** (100.6 MHz, CDCl_3 , 25 °C): δ = 18.3, 18.7, 24.3, 25.9, 31.8, 32.6, 46.3, 47.1, 48.3, 70.3, 72.2, 118.8, 122.1, 128.7, 139.6, 155.2, 163.7, 170.9. — **IR**: ν = 3330, 3223, 2721, 1656, 1623, 1567, 1504, 1398, 1311, 1214, 1200, 1178, 1123, 1083, 1034, 970. — $\text{C}_{20}\text{H}_{28}\text{N}_4\text{O}_3$ (372.46): calcd. C 64.49; H 7.58, N 15.04; found C 64.67, H 7.30, N 14.99.

1-((R)-3-((S)-4-Isopropyl-4,5-dihydrooxazol-2-yl)-1-oxo-1-(pyrrolidin-1-yl)propan-2-yl)-3-phenylurea (16). According to the general procedure, product **16** was yielded as yellow solid (0.074 g, 0.20 mmol, 58%) starting from precursor **25b** (0.134 g, 0.34 mmol).

R_f = 0.43 (DCM/MeOH 95:5). — m.p. 126–127 °C — $[\alpha]_D^{20}$ = -13.76 (c = 0.1, CHCl_3) — **¹H NMR** (400 MHz, CDCl_3 , 25 °C): δ = 0.83 (d, 3H, J = 6.7 Hz), 0.87 (d, 3H, J = 6.7 Hz), 1.65 (m, 1H), 1.88 (m, 2H), 1.97 (m, 2H), 2.67 (dd, 1H, J = 15.6, 6.6 Hz), 2.81 (dd, 1H, J = 15.6, 8.3 Hz), 3.42–3.55 (m, 2H), 3.83–3.93 (m, 4H), 4.19 (dd, 1H, J = 8.7, 7.9 Hz), 5.23 (m, 1H), 6.89 (d, 1H, J = 9.5 Hz), 6.94 (t, 1H, J = 7.3 Hz), 7.21 (t, 2H, J = 7.7 Hz), 7.35 (d, 2H, 7.8 Hz), 8.35 (s, 1H). — **¹³C NMR** (100.6 MHz, CDCl_3 , 25 °C): δ = 18.2, 18.4, 24.3, 25.9, 31.9, 32.4, 46.3, 47.1, 48.0, 70.2, 72.1, 118.8, 122.0, 128.7, 139.8, 155.1, 163.9, 171.0. — **IR**: ν = 3312, 2729, 1678, 1634, 1603, 1593, 1549, 1334, 1212, 1150, 1115, 1084, 1065, 991, 840. — $\text{C}_{20}\text{H}_{28}\text{N}_4\text{O}_3$ (372.46): calcd. C 64.49; H 7.58, N 15.04; found C 64.71, H 7.44, N 14.81.

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